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Review

Excited delirium syndrome (ExDS): Treatment options and considerations

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ABSTRACT

The term Excited Delirium Syndrome (ExDS) has traditionally been used in the forensic literature to describe findings in a subgroup of patients with delirium who suffered lethal consequences from their untreated severe agitation.(1-5) Excited delirium syndrome, also known as agitated delirium, is generally defined as altered mental status and combativeness or aggressiveness. Although the exact signs and symptoms are difficult to define precisely, clinical findings often include many of the following: tolerance to significant pain, rapid breathing, sweating, severe agitation, elevated temperature, delirium, non-compliance or poor awareness to direction from police or medical personnel, lack of fatiguing, unusual or superhuman strength, and inappropriate clothing for the current environment. It has become increasingly recognized that individuals displaying ExDS are at high risk for sudden death, and ExDS therefore represents a true medical emergency. Recently the American College of Emergency Physicians (ACEP) published the findings of a white paper on the topic of ExDS to better find consensus on the issues of definition, diagnosis, and treatment.(6) In so doing, ACEP joined the National Association of Medical Examiners (NAME) in recognizing ExDS as a medical condition.

For both paramedics and physicians, the difficulty in diagnosing the underlying cause of ExDS in an individual patient is that the presenting clinical signs and symptoms of ExDS can be produced by a wide variety of clinical disease processes. For example, agitation, combativeness, and altered mental status can be produced by hypoglycemia, thyroid storm, certain kinds of seizures, and these conditions can be difficult to distinguish from those produced by cocaine or methamphetamine intoxication.(7) Prehospital personnel are generally not expected to differentiate between the multiple possible causes of the patient's presentation, but rather simply to recognize that the patient has a medical emergency and initiate appropriate stabilizing treatment. ExDS patients will generally require transfer to an emergency department (ED) for further management, evaluation, and definitive care. In this paper, we present a typical ExDS case and then review existing literature for current treatment options.

1. Introduction

The term Excited delirium syndrome (ExDS) has traditionally been used in the forensic literature to describe findings in a subgroup of patients with delirium who suffered lethal consequences from their untreated severe agitation.[1–5] ExDS, also known as agitated delirium, is generally defined as altered mental status and combativeness or aggressiveness. Although the exact signs and symptoms are difficult to define precisely, clinical findings often include many of the following: tolerance to significant pain, rapid breathing, sweating, severe agitation, elevated temperature, delirium, non-compliance or poor awareness to direction from police or medical personnel, lack of fatiguing, unusual or 'superhuman strength' and inappropriate clothing for the current environment. It has become increasingly recognised that individuals displaying ExDS are at high risk for sudden death, and ExDS therefore represents a true medical emergency. Recently the American College of Emergency Physicians (ACEP) published the findings of a white paper on the topic of ExDS seeking consensus on the issues of definition, diagnosis and treatment.[6] In so doing, ACEP joined the National Association of Medical Examiners (NAME) in recognising ExDS as a medical condition.

For both paramedics and physicians, the difficulty in diagnosing the underlying cause of ExDS in an individual patient is that the

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presenting clinical signs and symptoms of ExDS can be produced by a wide variety of clinical disease processes. For example, agitation, combativeness and altered mental status are produced by hypoglycaemia, thyroid storm and certain kinds of seizures, and these conditions can be difficult to distinguish from those produced by cocaine or methamphetamine intoxication.[7] Prehospital personnel are generally not expected to differentiate between the multiple possible causes of the patient's presentation, but rather simply to recognise that the patient has a medical emergency and initiate appropriate stabilising treatment. ExDS patients will generally require transfer to an emergency department (ED) for further management, evaluation and definitive care. In this article, we present a typical ExDS case and then review existing literature for current treatment options.

2. Case presentation

Police are called for a 34-year-old male who was found wandering in a public park while talking to himself and taking off his clothes. When approached by police, he is noted to be completely naked, sweating and speaking semi-coherently about aliens "trying to get" him. Bystanders who know him at the park report that he has been using methamphetamine, but that he has used it before without a similar reaction. When police approach, he becomes more agitated and aggressive and begins to yell loudly.

At this point, police call for Emergency Medical Services (EMS) backup and ask that they be prepared to initiate treatment for a possible ExDS. While EMS is en route, officers on the scene plan for a rapid take down and restraint. A TASER® Electronic Control Device (ECD) is used to incapacitate the subject, and two officers then place the wrists into handcuffs. Simultaneously, a third and fourth officer restrain each leg with a loose hobble. The subject is noted to be incredibly strong and difficult to restrain, even for multiple officers.

With the scene and subject now secured and placed on his side, paramedics immediately begin their assessment and treatment. The subject continues to struggle against restraints and yell incoherently. The paramedics note that on examination, his skin is very hot to the touch. Vital signs include a heart rate of 130 beats per minute, a blood pressure of 143/67, a respiratory rate of 30 and an oxygen saturation of 100%. He is placed into a waiting ambulance for transport to the nearest ED.

Given these findings, a number of questions arise as to the appropriate treatment. First, what is the appropriate prehospital assessment and treatment for this subject? Should prehospital personnel administer sedatives or other medications? If so, what are the best medication options? Second, what is the appropriate treatment and diagnostic work-up for this subject when he arrives in the ED? We will now review each of these questions in turn, as well as appropriate treatment options.

3. Why is emergent treatment needed?

The concept of excited delirium has become a matter of increasing concern for law enforcement, emergency physicians, EMS personnel and others who encounter and manage these patients.[8] Although most patients with ExDS will survive, there still is a high fatality rate around 10%. Earlier recognition, intervention and proactive treatment might result in fewer deaths from this syndrome.

4. Work-up and treatment options for ExDS

The main difficulty in management of ExDS is usually not in the diagnostic approach, but rather in the safe initial management of these severely agitated patients who have an undifferentiated but potentially life-threatening syndrome. In general, non-coercive de-escalation techniques are preferred initially with all agitated patients.[9] In practice, this means verbal intervention with the patient without medication. However, patients with ExDS typically have altered mental status, and by virtue of this, are difficult to interact with verbally. However, efforts should still be made to reduce the patient's fear from the chaotic environment (police dogs, lights, sirens, shouting, etc.) if possible. Anecdotally, fearful patients who are experiencing catecholamine surges and are often on illicit drugs are unlikely to respond to compliance techniques, and the amount of force needed to restrain the patient will likely be far greater.

When approaching any agitated patient, including those suffering from ExDS, the staff should always be protected from the patient. Second, the patient should be protected from himself. In particular, this means that the airway should be protected during restraint, especially if the patient requires forceful restraint. As forceful restraint is nearly always required with ExDS patients, medication is often required early in the patient interaction.

Appropriate medication for patients with ExDS generally consists of three classes: benzodiazepines, antipsychotics (both first-generation and second-generation) or a dissociative agent such as ketamine. (See Table 2) As discussed below, many practitioners routinely administer both antipsychotics and benzodiazepines together. Although there are no randomised controlled trials of these different medication classes in patients with ExDS, the benefits and risks of each have been extrapolated from other patient populations.

5. Benzodiazepines

Benzodiazepines such as lorazepam, diazepam or midazolam bind to gamma aminobutyric acid (GABA) receptors, which are the main inhibitory transmitter in the human brain. The use of this class of medications is therefore extremely helpful in management of severely agitated ExDS patients, especially if the source of the agitation is thought to be stimulant intoxication. Medication classes, routes and dose information are listed in Table 1. Benzodiazapines may be given parenterally by the intramuscular (IM), intravenous (IV) or intraosseous (IO) route. Alternate dosing may be used with intranasal (IN) midazolam if IV or IO access is initially unavailable. Serial doses may be required to maintain sedation or anxiolysis, and doses of benzodiazepines are typically much higher in ExDS patients than those routinely used in treatment of agitated or anxious persons. Disadvantages of benzodiazepines include relatively slow onset if given by the IM route (1–5 min for midazolam), over-sedation or respiratory depression, synergism with alcohol or other sedative/hypnotics and hypotension. Another problem is the relatively wide range of dose; hence, finding a therapeutic window without causing respiratory impairment in a single dose can be difficult.

Table 1
ExDS brief differential diagnosis.

Substance intoxication
Substance withdrawal
Hypoxia
Electrolyte disturbances
Thyroid storm
Infection
Seizures
Head injury
Heat stroke
Serotonin syndrome
Neuroleptic malignant syndrome

Table 2
Medication treatment options.

Medication (Trade Name)	Administration routes	Typical Dosing (mg)	Onset (min)	Duration (min)
Benzodiazapines				
Midazolam (Versed)	IN	5	3–5	30–60
	IM	5	10–15	120–360
	IV	2–5	1–5	30–60
Lorazepam (Ativan)	IM	4	15–30	60–120
	IV	2–4	2–5	60–120
Diazepam (Valium)	IM	10	15–30	15–60
	IV	5–10	2–5	15–60
Antipsychotics				
Haloperidol (Haldol)	IM	10–20	15–30	180–360
	IV	5–10	10	180–360
Droperidol (Inapsine)	IM	5	10–30	120–240
	IV	2.5	10	120–240
Ziprasidone (Geodon)[a]	IM	10–20	15–30	240
Olanzapine (Zyprexa)[a]	IM	10	15–30	24 h
NMDA receptor antagonist/Dissociative ketamine (Ketaset, Ketalar)	IM	4–5 mg/kg	3–5	60–90
	IV	2–4 mg/kg	1	20–30

[a] Atypical antipsychotic medications.

6. Antipsychotics

Both typical and atypical antipsychotic agents have been used in the treatment of ExDS. These agents are Food and Drug Administration (FDA) approved for IM use but are also commonly administered IV. First-generation antipsychotics such as haloperidol or droperidol generally bind tightly to dopamine receptors with little activity at other receptor sub-types. Second-generation antipsychotics such as ziprasidone and olanzapine have more variable action at other receptor types and so have more variable side effects.

Some ExDS deaths have been thought to be related to ventricular dysrhythmias and sudden cardiac death related to lengthened QT intervals. Most documented ExDS cardiac arrests that occur while a patient is on a monitor or monitored quickly after arrest are found to have asystolic or ventricular escape rhythms. Therefore, QT syndrome degenerating to a ventricular fibrillation (VF) or ventricular tachycardia (VT) as the cause of death in patients with ExDS is unlikely. However, if long QT syndrome is suspected based on known patient history, clinicians should be cautious with first-generation antipsychotics such as haloperidol or droperidol. The FDA has required labelled a 'black box' warning for droperidol regarding QT prolongation and risk for ventricular dysrhythmias such as torsades de pointes. Therefore, cardiac monitoring is appropriate when using these medications, when reasonable. This risk does not seem as great with second-generation antipsychotics, although there are few studies of this class of medication in agitation not from psychiatric origin.

Potentially more concerning here is the issue of hyperthermia. There is some concern that the hyperthermia seen in these cases may come from specific transport dopamine derangements as occurs in neuroleptic malignant syndrome (NMS). Therefore, using these agents could be argued as contraindicated on a theoretical basis. However, there is a vast experience with using these in undifferentiated agitation in ED patients with an excellent safety record and many feel that the need to reduce agitation in a dangerously agitated patient outweighs this risk.

7. Ketamine

Ketamine, a dissociative anaesthetic that acts as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is an older drug that has found recent use in ExDS. The drug has a long history of safe use in the ED setting, particularly for procedural sedation or as an induction agent for intubation, particularly in asthma patients.[10] Ketamine may be given IM or IV and rapidly causes a dissociative anaesthesia with preservation of airway reflexes. While ketamine can cause or worsen pre-existing hypertension and tachycardia, which could be problematic in ExDS patients, case reports have indicated excellent clinical results and overall reductions in hyperadrenergic vital signs, presumably due to dissociative sedation, when used with ExDS patients in the prehospital setting.[10–13] Other potential side effects include increased oral secretions, laryngospasm and emergence phenomena. The great benefit here is a very rapid onset of action, preservation of airway reflexes and a large safety range that allows administration of large doses without titration.

8. Combination therapy

Many practitioners have found it useful to pair benzodiazepines with antipsychotics, as behavioural calming appears to be synergistic when these medications are used together. In 1997, Battaglia and colleagues published the largest ED study of haloperidol and lorazepam.[14] In this study, the incidence of side effects from haloperidol use was dramatically reduced when combined with a benzodiazepine such as lorazepam. A later Cochrane review also noted a reduction of side effects with adjunctive meds, and clinicians should always consider administering haloperidol with either a benzodiazepine or an anticholinergic such as promethazine.[15] However, the Battaglia study specifically excluded individuals with alcohol intoxication, and hence it is unknown whether this combination would be useful in intoxicated patients with ExDS. As with any class of medications, patients should be monitored for sedation and respiratory depression.

Other practitioners have described using IM ketamine for initial therapy, followed by benzodiazepines once physical control and IV access are achieved. These agents are also thought to have synergistic effects, with the additional benefit of transition to a primarily benzodiazepine sedation mitigating any potential emergence phenomena as the short-acting dissociative agent is metabolised.

9. Supportive treatment

A goal of calming with antipsychotics, benzodiazepines or the combination of these medications is to properly assess the patient. Definitive treatment of ExDS involves treatment of the underlying condition producing the ExDS. The wide range of clinical signs and symptoms of patients with ExDS means that a wide range of possible alternative diagnoses should be considered (see Table 1). In the ED, labs and imaging should be considered as part of the diagnostic work-up.[8] Treatment is generally supportive, and involves IV fluids, sodium bicarbonate and/or cooling measures.

9.1. IV Fluids

Patients with ExDS may present dehydrated due to decreased water intake complicated by increased sensible fluid loss from elevated temperature, hyperventilation and diaphoresis.[5] In addition, drugs that induce ExDS predispose patients to rhabdomyolysis and subsequent electrolyte abnormalities. IV fluid administration is therefore generally indicated in ExDS patients, although there is a theoretical risk of fluid overload causing a congestive heart failure (CHF) presentation in patients who may have a co-existing cardiomyopathy. Caution must be used during IV placement to avoid injury to the patient or caregivers, and IV access is not recommended until the patient is appropriately calm. I/O access might

be a good option as restraining a limb for this is usually easier and safer. IV fluid should consist of crystalloids such as normal saline, or lactated Ringer's solution, and patients may require several litres depending on clinical presentation.

10. Sodium bicarbonate

Routine supplemental use of continuous or intermittent boluses of sodium bicarbonate for treatment of metabolic acidosis in ExDS has not been prospectively evaluated. Severe acidosis and concurrent electrolyte abnormalities predispose to arrhythmias and may be treated with empiric sodium bicarbonate, unless hypokalaemia is suspected clinically. Even if not initially planning on using bicarbonate to treat acidosis, evaluation of pH status at the hospital can be an important piece of information. This value can be used both to direct therapy as well as document the severity of the patient's status, particularly if the patient ends up dying. This information is also useful for the forensic team in fatal ExDS cases.

Urine alkalisation with sodium bicarbonate combined with IV fluids may be initiated empirically or based on laboratory results to help prevent renal failure from rhabdomyolysis. However, the use of bicarbonate is not based on large amounts of experimental evidence, and so it must be employed after a carefully weighed risk–benefit analysis. Because of this, routine use in the prehospital setting is not widespread.

11. Cooling measures

Hyperthermia, defined as an elevated body temperature due to failed thermoregulation, is present in many patients with ExDS but need not be present to make the diagnosis. In cocaine and methamphetamine-using ExDS patients, it is thought to be related to the dopamine derangements.[16] In lieu of a rectal temperature, a tactile temperature may be used for a rough assessment until safe assessment of a core temperature measurement becomes possible.[5] If elevated temperature is present, there are several potential treatment options including external cooling, cooled IV fluids or ice packs applied to the neck, groin or axilla. Other methods for cooling include disrobing the patient if they were still clothed, placing in a cool environment, misting across bare skin, evaporative cooling with tepid water and fans or an ice bath immersion.[17,18] Many of these methods may be impractical in a prehospital setting and already established EMS standard heat illness protocols are acceptable treatment approaches. Patients with significant temperature elevations suggestive of heat stroke may be placed in an ice bath and transitioned to other methods listed above. The patient's altered mental status will prevent self-reporting of temperature status; hence, caregivers should serially monitor the temperature so as not to overuse cooling methods and make the patient hypothermic. There are few risks to the cooling methods listed above, but providers should document an elevated temperature first if cooling measures are to be initiated. Palpated or tactile temperature assessment is probably reasonable in the field but a core temperature should be obtained once the patient is restrained and sedated and safe to obtain.

12. Discussion

ExDS is a clinical syndrome that is not universally fatal, though the fact that the pathology literature is more robust on this topic tends to bias the discussion towards its lethality. Nonetheless, a proportion of patients will progress to cardiac arrest and death as a result of a combination of factors in the disease that are not fully understood.[2,16,19–21] While many of the current deaths from ExDS are likely not preventable, there may be an unidentified subset in whom death could be averted with an early directed therapeutic intervention. Initial documentation of clinical observations by police, EMS and ED personnel is important in reporting how acutely ill and at risk for sudden death the patient was when encountered and can assist medical examiners and case reviewers in better understanding the presentation and identify the probability that the patient was experiencing ExDS.

Tactics used in the prehospital setting to control a patient in ExDS should revolve around patient and provider safety with rapid control and minimisation of the patient's exertional activity. The use of an electronic control device, such as a TASER® ECD, to gain control of a patient appears preferable to the more traditional and drawn out approach of going 'hands on', as fighting or heavy physical exertion has more of a deleterious effect on a patient's already tenuous acid–base status.[22–24] Thus, heavy exertion may make the patient more acidotic and contribute to a greater risk for sudden death compared with a short burst of electrical control and rapid restraint. Judicious restraint of the patient will prevent ongoing use of the large thigh and arm muscles, which consume oxygen and contribute to acid–base disturbances. Containment and de-escalation where possible will minimise both stress and exertion.

Increased awareness of ExDS among medical personnel and law enforcement personnel will hopefully lead to better early recognition of individuals experiencing this medical crisis and lead to early interventions that prevent sudden death. Co-operative protocols that combine law enforcement and EMS efforts to manage these patients should be encouraged. At this point, there is broad consensus that early medical intervention should include rapid control, aggressive sedation, hydration, monitoring and transport of patients who display signs and symptoms of ExDS. Further research is needed to help define the disease process itself, mechanisms and risk factors for sudden death and optimal therapeutic approaches to improve outcomes.

Conflict of interest

None of the authors have any personal or financial relationships that would constitute a conflict of interest regarding the information presented in this paper.

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